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LISA A HAILE PH D
GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1600
SAN DIEGO, CA 92121

EXAMINER
GOLDBERG, JEANINE ANNE

ART UNIT	PAPER NUMBER
1634	21

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/398,522	Applicant(s) ISSA, JEAN-PIERRE	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 16-38* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 25-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10, 16-24, 33-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed August 21, 2002. Currently, claims 1-10, 16-38 are pending. Claims 1-9, 25-32 have been withdrawn from consideration as drawn to non-elected claims. This action is FINAL.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10, 16-24, and Newly added 33-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for detecting cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the methylation state of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and CACNA1G gene such that a cellular proliferative disorder may be detected by detection of hypermethylation.

The specification teaches that aberrant methylation of CGIs have been detected in genetic disease such as the fragile-X syndrome, in aging cells and in neoplasia (pg. 3, lines 21-23). The specification teaches CpG-rich regions from APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 which are hypermethylated (pg. 7, lines 10-11, Figures 4A-4F). Table 5 of the specification states that the genes are "differentially methylated in disease versus normal tissue" (page 39). Further, Figure 4 illustrates the CpG islands for each of these genes. The specification teaches that methylation analysis of CACNA1G was performed (pg. 24). The specification teaches that certain regions of CACNA1G are differentially methylated between tissue types. For example, regions 1 and 2 are not methylated in gliomas, region 3 is not methylated, 5,6 and 7 are more or an all or none methylation situation and regions 4 and 8 are part in breast/colon cell lines..

The art teaches that tissues are both hyper and hypo methylated as indicative of cancerous tissue. Balyin et al. (herein referred to as Balyin-1) teaches alterations in DNA methylation as a fundamental aspect of neoplasia (Advances in Cancer Research, Vol. 72, pg. 141-196, 1998). Baylin-1 discusses not only hypermethylation as associated with cancer, but additionally teaches that hypomethylation is associated with cancer. In the discussion, Baylin-1 teaches that in a number of models of carcinogenesis decrease in numbers of methyl groups appear to begin early in tumor progression and before the appearance of frank tumor formation (pg. 151). Baylin teaches that there is a clear association of DNA hypomethylation with tumors, however, the exact ramifications of this change for steps in tumor progression are poorly

understood (pg. 151). Hypomethylation patters have been described for oncogenes in tumors. Baylin also teaches hypermethylation in cancer (pg. 152). Baylin provides several examples of CpG island hypermethylation associated with transcriptional inactivation of specific genes in neoplastic cells including Rb, VHL, p16, p15, E-cadherin, hMLH1, and ER (Table 2). Further, Nelson et al. (herein referred to as Nelson) teaches a method for detecting proliferative disorder associated with glutathione-S-transferase (GSTP1) which detect hypermethylation of GSTP1 promoter in a tissue sample (abstract). As seen in Figure 5, hypermethylation does not appear to occur in normal tissues. Nelson teaches that a hypermethylated promoter for the human GSTP1 positively correlates with prostatic carcinogenesis (col. 3, lines 5-10). In a distinct article, Baylin et al. (herein referred to as Baylin-2) teaches that HIC-1 is within a CpG island which is abnormally methylated in many different types of tumors. Baylin-1 teaches hypermethylation of HIC-1 was analyzed in primary tumors and cultured cells lines (col. 22, lines 36-40).

Moreover, the art teaches analysis of CACNA1G, PITX2, GPR37 and SDC4 with respect to acute myeloid leukemia (Toyota et al. Blood, Vol 97, No.9, pages 2823-2829). Toyota specifically illustrates that normal bone marrow was analyzed and no significant methylation (2% of greater) was observed in any of the genes analyzed (page 2825, col 2). Toyota also provides distribution of methylation densities for CpG islands of 15 selected genes among 36 acute myeloid leukemia patients (page 2826). The table 2 illustrates the frequency of the methylation density of SDC4, GPR37 and PITX2 as frequently above 10% methylation. The table also clearly illustrates that

approximately 92% of the patients had below 2% methylation density, which was indicated as not significant. Therefore, CACNA1G does not appear to be methylated significantly among AML patients.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification does not provide enabling disclosure directed to detecting hypermethylation of any CpG island within the genes as indicative of cellular proliferative disorder. The specification has identified very specific CpG islands within the genes for hypermethylation. The specification does not appear to illustrate that any CpG island within the gene is associated with cellular proliferative disorders. It is unpredictable which CpG islands are differentially methylated and which CpG islands do not show any correlation with cellular proliferative disorders. Therefore, undue experimentation would be required to assess whether additional CpG island methylation allows for detection of cellular proliferative disorders. As seen in the example directed to CACNA1G, the specifically illustrates that certain CpG islands do not have methylation and are not associated with cellular proliferative disorder, for example region 3 (page 25). It is unpredictable which CpG islands are associated with cellular proliferative disorders.

Secondly, the specification illustrates generically that different genes are found to be differentially methylated in differed tissues. It is unpredictable that each and every gene is differentially methylated in every tissue encompassed by nucleic acid containing specimen. As provided within the instant specification, regions 1 and 2 were not methylated in gliomas (page 25). Thus, the specification illustreates that absent undue

experimentation, it is unpredictable which CpG islands are associated with various tissues.

Moreover, cellular proliferative disorder very broadly defined in the specification such that it is unpredictable that the genes claimed would have any relationship to some of the diseases. Cellular proliferative disorders has been defined broadly in the specification to include, but are not limited to, low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, colorectal cancer, colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma (pabe 30, lines 22-26). The specification has not broadly enabled the detection of each of these cellular proliferative disorders with a representative number of CpG islands such that the skilled artisan would clearly recognize the broad applicability to each of the disorders. Furthermore, Table 5 appears to indicate that not all genes are associated with each and every disease. Certain genes which are hypermethylated are specific to certain disorders. Similarly, the art appears to support that hypermethylation in AML varies among genes.

The specification has not provided any correlation between tumor and normal tissue regarding hypermethylation for APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders. It would be unpredictable to what degree these specific genes are infact differentially methylated in cancerous tissue and normal tissue. And it would require undue experimentation for

the skilled artisan to perform the necessary experimentation to determine whether the listed genes are only hypermethylated in specific tumors and other cellular proliferative disorders such that cellular proliferative disorder may be detected. The skilled artisan would be required to sample tumor and normal cells from a clinical study to ascertain whether the tumors are hypermethylated and then determine whether this is only observed in tumors. Genes are known to be methylated at certain stages, however, mere methylation is not necessarily indicative of cellular proliferative disorders. Absent showing that these genes are in fact differentially methylated in tumors and normal tissue, the skilled artisan would be unable to practice the claimed invention without undue experimentation. The specification does not appear to provide whether the samples were studied in all tumors, namely common tumors, leukemias, breast, prostate, and colon tumors, however were only hypermethylated in certain tissues and not in other tissues. The claims are not limited to the CpG islands which the specification has shown in Figure 4, but rather the gene as a whole or associated regulatory regions of the gene.

No information regarding the number of normal samples which were compared with the tumor samples. The specification has not provided any showings that a representative number or statistically significant number of the genes showed aberrant methylation such that cellular proliferative disorder would be indicated. It is unclear whether one sample was studied which had hypermethylation or whether a representative sample was reviewed to provide a representative analysis of the hypermethlyation of tumors. Moreover, from Table 5 it is unclear whether the tumor

samples were from patients, were cell lines or of other origin. Additionally, within Table 5, the specification cites that the genes were hypermethylated in "common tumors" however, it is unclear what "common tumors" encompass and what common tumors do not encompass.

Response to Arguments

The response traverses the rejection. The response asserts that "the specification recites the nucleotide sequence of a CpG island for 14 different genes, as recited in Claim 10, and for each of these genes, discloses at least one type of cancer in which the recited CpG island is hypermethylation (see specification, Table 5)." This argument has been reviewed but is not convincing because the turning to Table 5, several of the listed genes are methylated in "common tumors" however, as provided in the rejection above, it is unclear what "common tumors" encompass and what common tumors do not encompass. Moreover, each of the listed genes appears to be methylated only in certain tissues and not in cancerous tissue generally.

As provided in the rejection above, "Table 5 appears to indicate that not all genes are associated with each and every disease. Certain genes which are hypermethylated are specific to certain disorders." It is clear from the post filing date are that genes which are hypermethylated in certain cancers are not hypermethylated in all cancers. As provided by Moinova et al. (PNAS, Vol. 99, No. 7, pages 4562-4567, April 2002), HLTF methylation was analyzed in primary colon cancer tissues and found to be methylated, however, no methylation of HLTF was detected in breast or lung cancers. Similarly, Kazuhiro et al. (Clinical Cancer Research, Vol. 8, No. 10, pages 3164-3171,

abstract only) teaches that MLH1, HRK and CACNA1G are not methylated in oral squamous cell carcinomas. Therefore, a gene which is found to be methylated on one type of cancer is not predictably methylated in all types of cancers. Therefore, absent additional experimentation it is unpredictable which cancers each of the genes of the instant claims are associated. The assertion in the response that each of the genes are hypermethylated in at least one cancer does not enable the full scope of the claims.

The response asserts, page 6, that cellular proliferative disorder has been added to Claim 33, directed to CACNA1G. The response states that the specification teaches hypermethylation of numerous cacners and cellular proliferative disorders, but not normal tissue (page 27 of the specification). First, as discussed above, CACNA1G is not methylated in oral squamous cell carcinomas. Therefore, the broad scope of the claim is not enabled. Second, as pointed out in the response, not all subregions of CACNA1G are hypermethylated in all cancers, for example gliomas. Third, as illustrated in the response, CACNA1G is hypermethylated in a benign condition, therefore, comparing hypermethylation of normal and samples will not be indicative of cancers, since hypermethylation is also associated with benign conditions.

The response asserts that "it is not necessary to demonstrate that the CACNA1G CpG island is hypermethylated in every cellular proliferative disorder." The examiner agrees with the response, however, it is unpredictable based upon the teachings in the art and the specification, which cellular proliferative disorders are associated with hypermethylation and which CpG subregions are associated with cancers since the art teaches that there are cases in which genes are not associated with all cancers. The

skilled artisan would be required to perform undue experimentation for each cancer he wished to consider to determine whether there was an association between the specific CpG island and a specific cancer.

With respect to applicant's discussion of Toyota, the examiner acknowledges that the presence of hypermethylation of some AML patients is commensurate in scope with the claims.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. No claims allowable.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is

(703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
November 5, 2002

W. Gary Jones
Supervisory Patent Examiner
Technology Center 1600